ACC.11
60th Annual Scientific Session & Expo

E1481
JACC April 5, 2011
Volume 57, Issue 15

VASCULAR DISEASE

EFFECT OF CILOSTAZOL ON ENDOTHELIAL PROGENITOR CELLS AND HYBRID THERAPY IN MURINE HINDLIMB ISCHEMIA

ACC Poster Contributions
Ernest N. Morial Convention Center, Hall F
Sunday, April 03, 2011, 3:30 p.m.-4:45 p.m.

Session Title: Cell Therapy and Cardiovascular Diseases
Abstract Category: 9. Vascular—Pathophysiology—Basic/Angiogenesis/Gene Therapy
Session-Poster Board Number: 1042-112

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Background: We and others have reported that cilostazol could promote angiogenesis. In this study, we investigated the effects of cilostazol on endothelial progenitor cells (EPCs) and hybrid therapy in murine hindlimb ischemia.

Methods: Cilostazol was added 3 days after isolation and culture of human early EPCs. Colony-forming units were counted 7 days later. Total ribonucleic acid was extracted from EPCs treated with cilostazol and subjected to reverse transcription-polymerase chain reaction analysis of endothelial NO synthase (eNOS), vascular endothelial growth factor-receptor 2 (VEGF-R2), and CD31. Eight-week-old male SCID mice were divided into 4 groups (vehicle, EPCs only, cilostazol only, and EPCs plus cilostazol, respectively). 1×106 of culture-expanded EPCs were transplanted by multiple intramuscular injections one day after hindlimb ischemia. Single doses of cilostazol (10 mg/kg) were injected intraperitoneally before hindlimb ischemia and 2 times per day for 7 days.

Results: Cilostazol (30 μM) treatment significantly increased colony-forming units of EPCs by 2.5 folds (25.2±0.9 vs 10.8±0.5 cells/well, $p<0.05$) and expression of eNOS, VEGF-R2, and CD31 as compared to negative control. Blood flow recovery ratio and capillary density after 14 days in the ischemic hindlimb were highest in EPCs plus cilostazol-treated mice (0.68±0.09; 3588±78 particles/mm2) than cilostazol only (0.48±0.01; 2991±49 particles/mm2), EPCs only (0.35±0.03; 2788±49 particles/mm2), and vehicle (0.21±0.02; 2010±11 particles/mm2, all $p<0.05$ vs vehicle, respectively), which were attenuated by an eNOS inhibitor injection. Hybrid therapy had the upmost effect on phosphorylation of eNOS and Akt in ischemic muscle. Human CD31+ cells were mostly located around but far from host capillaries in EPCs only; however, they formed more capillaries with host endothelial cells in hybrid therapy.

Conclusions: Cilostazol has significantly beneficial effect on endothelial differentiation in EPCs. It promotes vasculogensis of transplanted human EPCs in murine hindlimb ischemia partly mediated by activating Akt/eNOS signaling pathway and enhancing incorporation of EPCs into neovascularization site.